particular attention to each of these findings and evaluated the patients throughout the development program for these.

We also saw that with longer durations of dosing there were no new findings and no progression of previously identified treatment related effects, and in a battery of experiments, no general toxicity was observed.

Clinically, 623 individuals received caspofungin, including approximately 550 who received multiple doses with the distribution listed here. Four hundred and twenty received the recommended dosing regimen or higher for at least seven days, including subjects in clinical pharmacology, as well as patients with Candida aspergillosis infections, in a small number of patients who received treatment with longer courses of therapy defined as at least 28 days.

The safety data are from final case report form data from the Phase I studies, as well as the completed Phase II and III studies in candida, and the salvage aspergillus study.

We also have information available on serious adverse experiences reported in Merck's worldwide adverse experience system, including blinded data from the invasive candidiasis and empirical

therapy studies, as well as data from the compassionate use program.

Overall, across all 600 individuals who have received caspofungin, caspofungin has been well tolerated. This has been included in patients with a wide spectrum of diseases and a number of concomitant medications. Favorable safety profile has been maintained with extended therapy, defined as those who have received at least 28 days of dosing.

There have been few serious drug related adverse experiences or discontinuations due to drug related adverse experiences.

Elevations in serum transaminases have occurred at a frequency similar to the comparators of fluconazole and amphotericin B.

We have also looked specifically for allergic reactions. We've looked for evidence of histamine reactions because of the findings in the preclinical safety studies, as well as allergic reactions which could potentially be related to covalent binding.

And in the individuals treated, symptoms compatible with histamine release have been infrequently noted. Most have been local dermatologic reactions, often at the site of infusion with these

patients often difficult to tell if it's irritation or local histamine release, rarely with fever and other findings.

There has been one individual in the compassionate use program recently treated who, during the first dose of caspofungin therapy developed symptoms which were compatible with a systemic acute histamine release.

We have also looked, as I mentioned, for evidence of allergic reactions and have looked across all of the studies for things such as fever, rash, and eosinophilia. These have occurred, but they've been uncommon, and they've rarely occurred together.

Because of these patients having underlying HIV infection, hematologic malignancies or transplants, the underlying diseases or concomitant illnesses are commonly associated with these findings, and patients are often receiving concomitant medications known to be associated with these findings.

In addition, it's important to note that the findings, when they occurred, were often isolated events and resolved during continued caspofungin therapy.

So in summary, in looking across carefully

at all of the patients in the program, we have not seen a pattern of findings that were suggestive of allergic reactions.

As I mentioned, we've also looked at other clinical and laboratory adverse experiences. What I'd like to do now is to turn to drug related clinical and laboratory adverse experiences first in the candida studies and then in the aspergillus studies.

We've looked at drug related adverse experiences because of the high background rate of adverse experiences in these patient populations. This slide displays combined the two Phase II studies in Candida esophagitis, which the comparator was amphotericin B, as well as the Phase III candida study in which caspofungin at 50 milligrams was compared to fluconazole.

You can see the most common clinical adverse experiences were fever and phlebitis. If we look at the incidence of other clinical adverse experiences, you can see they occurred at rates similar to fluconazole and are less common than amphotericin B.

One of the things that I do want to point out with combining the studies together is that this slide shows, as you may have noticed, it appeared as

though there may be a drug dose related increase in fever, and when you look at each of the individual studies -- and this is the two Phase II studies that I mentioned and the Phase III study -- you can see that the incidence of drug related fever, as well as the incidence of fever overall is similar across caspofungin groups and is less than amphotericin B.

And, in fact, in the Phase III study, which is the largest, with approximately 85 patients per group, the incidence of drug related fever was similar to that seen with fluconazole.

This next slide displays in a similar fashion drug related laboratory adverse experiences, again, for all of the candida studies. You can see that the incidence of adverse experiences is similar to what's seen with fluconazole.

I do want to point out if we look at elevations in serum creatinine, there were few individuals who had elevations in creatinine during the course of caspofungin therapy, but only one individual was considered by the investigator to have an elevation which was possibly drug related, and that's this individual.

This patient had underlying diabetes mellitus and hypertension, had an elevated creatinine

and an abnormal urinary sediment at baseline, and had an increase in creatinine which was felt to be possibly related to drug.

This is in contrast to amphotericin B in which 28 percent of patients had an elevation in creatinine felt to be drug related in the blinded studies, and you see a very low incidence of elevations in creatinine and fluconazole as would be expected.

So, in summary, across the controlled candida studies, there's no dose related toxicity noted. The most common drug related clinical adverse experiences were fever and phlebitis or infused vein complications, but these rarely limited therapy.

There were no serious drug related adverse experiences and few drug related adverse experiences that led to discontinuation of therapy.

If we turn now to the aspergillus study in which patients were more acutely ill and required longer term therapy, we see that the safety profile is similar to that seen in the controlled candida studies. Drug related clinical and laboratory adverse experiences were uncommon.

There were two serious adverse experiences which were considered by investigators to be drug

related. The first is a 37 year old man with refractory multiple myeloma who had undergone an allogeneic bone marrow transplant, was being treated for pulmonary aspergillosis, actually was discharged and being treated as an out-patient, when on day 21 he returned to the hospital with dyspnea and pulmonary infiltrates.

The patient was treated with the gancyclovir trimethoprim sulfa, high dose corticosteroids, and the caspofungin was stopped. Because a specific etiology was not identified on bronchoscopy, the investigator felt that this was possibly drug related.

The second is hypercalcemia, which occurred in a patient with widespread lymphoma and disseminated aspergillosis involving the spine. When the increased calcium initially occurred, the investigator felt it may be due to the patient's underlying disease or lymphoma, but as additional information was obtained later, the patient was not found to have a relapse or have increase in calcium with worsening of the aspergillus. The hypercalcemia was considered to be probably related to drug.

We've looked carefully at the rest of the safety database and do not see hypercalcemia as a

problem.

Caspofungin has also been generally well tolerated in the 27 patients who have received longer term therapy, including an individual who received treatment for as long as 162 days. In the safety profile, the 11 additional patients, was similar to that seen in the original 58.

If we look now at the specific drug related clinical and laboratory adverse experiences that were reported in more than one patient, we see that the clinical adverse experiences were similar to those seen in the candida studies.

There were two individuals with increased eosinophils, one patient with good pastures (phonetic) in a kidney transplant who had an isolated elevation in eosinophils during treatment, which resolved with continued therapy, and a second who had an increased eosinophil count in the setting of GMCS when all of their cell lines increased.

So, in summary, across all of the data in the 600-plus patients available, caspofungin has had a favorable safety profile to date. There have been few serious drug related adverse experiences, few drug related adverse experiences leading to discontinuation.

The incidence of drug related elevation in liver enzymes is low, and caspofungin is relatively free of significant drug interactions.

This concludes my summary of the data which demonstrates that caspofungin is safe and effective in the treatment of patients with invasive aspergillosis, and I'd like to turn over to Dr. Chodakewitz for concluding remarks.

Thank you.

DR. CHODAKEWITZ: You've heard Dr. Sable summarize a large body of information from our development program with caspofungin, and more information has been provided in more detail in the background package which was circulated to the Advisory Committee members.

We believe that this body of information as a whole allows several important conclusions to be drawn. First, that caspofungin represents the first of a new class of antifungal agents, and that it works by a novel mechanism of action, specifically inhibiting cell wall synthesis in clinically important pathogens.

And based on Dr. Perfect's comments, we think that that offers potential advantages.

As has been summarized by Dr. Sable, we

think that there's clear efficacy of caspofungin in the treatment of patients with aspergillus who are refractory to or intolerant of standard agents. This remains a disease with very high mortality, as you've seen, and also a group of patients who often have limited therapeutic options.

Lastly, but I think also very importantly for the clinical utility of the drug, it's a compound that has demonstrated a very favorable safety profile.

Now, in her introductory comments, Dr. Goodrow mentioned several aspects less common of the drug or the development program, and now that you've heard Dr. Sable's presentation, I think it might be useful to just touch briefly on a few of those with the goal of trying to put them in clinical perspective.

And there are three of those aspects that I'd like to come back to.

One, antimicrobial activity of caspofungin against aspergillus;

Secondly, some of the properties of caspofungin related to distribution and metabolism;

And, lastly, specifically the size of our efficacy database for aspergillosis.

I just want to touch on each of these

briefly.

As has been discussed, there are clear in vitro effects of caspofungin across candida and aspergillus species. For candida,, the drug meets the standard definitions of a fungicidal agent, but that's not as clearly the case for its activity in vitro against aspergillus.

As we've explored this further, in fact, we believe that these observations are very consistent with the drug's mechanism of action, and in fact, there's really no a priori reason why we would necessarily expect a new agent with a new mechanism of action to fit neatly into one of these definitions.

And so I think it's also important to put these observations in an in vivo context be it from animal models or from patients.

As you've seen, our results with caspofungin in animal models, including quite immunocompromised animals, demonstrate a sustained antifungal effect of the drug, and consistently that effect has been similar to that observed with amphotericin.

And lastly, and obviously most directly relevant, is that we've seen clear clinical responses in the kind of highly immunocompromised patients that

Dr. Perfect mentioned.

In looking at the drug's distribution and metabolism, I'd like to focus on two areas that I think try to address whether these properties are understood and impact the clinical use of the compound: pharmacokinetics and drug interactions.

First, as you've seen, the pharmacokinetics of caspofungin are really quite well defined and quite consistent across a range of patient populations.

In looking at drug interactions, we've utilized a two-prong approach, both formal Phase I drug interactions and extensive population PK sampling. We think the advantage of this approach is that the combination allows evaluation of concomitant use of caspofungin with a relatively large number of other compounds, and as you've seen, there are very few situations in which a dose modification appears to be required.

So we believe that these properties are well understood and that clear, simple dosing guidelines can be provided for the use of caspofungin.

Lastly, in thinking about an uncommon disease, particularly an uncommon disease with high mortality, acquiring sufficient clinical efficacy data

is always a challenge.

We've utilized, as have other compounds, a noncomparative trial in the setting of salvage aspergillosis, and as Dr. Sable explained, we've tried to incorporate strict criteria and a heavy dependence on our expert panel review to maximize the interpretability of the results that we've derived, and we believe that that's been successful; that the clarity of the efficacy data balances the relatively limited patient numbers in our program, and I think there's several reasons for that.

First, it has to do with certainty, both the diagnosis of patients with invasive aspergillosis and also the response to caspofungin therapy.

Secondly, it has to do with consistency. The consistency of the drug's response across a range of clinically important patient subpopulations.

And, lastly, as additional evidence has been accrued, be it from more patients going into our aspergillus study, our historical control study, or the use of the drug in other fungal infections, those results have reinforced the favorable response to caspofungin.

So, in fact, we believe that the answer to the adequacy of the efficacy database is, yes, it is

adequate because we believe clear conclusions regarding the drug's activity can be derived.

So some of the less typical aspects of caspofungin and some of the pitfalls of study design and the difficulty in evaluating drugs in this kind of disease have been carefully reviewed and thought about throughout our development program. We believe that the quality and consistency of the data is high, and it provides clear demonstration of the clinical efficacy of caspofungin.

And, similarly and importantly, it demonstrates that the drug has a very favorable safety profile.

Therefore, we feel that caspofungin represents an important therapeutic option for a group of patients who have a poor prognosis and often have limited therapeutic options, and our observations are very consistent with the indication which we are seeking, which is that caspofungin is indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Thank you.

ACTING CHAIRMAN GULICK: Thanks very much. We have time for questions of the sponsor.

Maybe, Dr. Sable, you'd like to join Dr. Chodakewitz at the mic.

Dr. Schapiro will start us off.

DR. SCHAPIRO: First of all, I'd like to thank you for the very detailed talk and the background material. I'm still not exactly sure how you came up with the dose of 50. It looked to me like the basis for that was an infection which is far less severe and a bug which may be more sensitive, and I wasn't clear why that was the dose that you decided to go forward with.

DR. SABLE: As I had mentioned in my presentation, the selection of dose for invasive aspergillosis was actually based on an integration of data with the clinical information, as you mentioned, coming from candida infections.

But just to go back and review the information we had, we saw that the in vitro susceptibility in MIC-90 for candida and aspergillus were similar at approximately one microgram per mL, and the dose that we selected of 50 milligrams daily actually maintains drug levels at or above that concentration throughout the 24-hour dosing interval.

The 70 milligram dose on day one allows that concentration to be achieved more rapidly. So

based on that, and the fact that we saw that the 50 milligram dose, there was no benefit of 70 over 50 in the candida studies, we felt that that was an appropriate dose to evaluate.

There was also at that point less information on 70 milligrams for a longer period of time, which of course over time we have accrued more data on the higher dose, but that was the basis for selecting the dose initially.

DR. SCHAPIRO: And based on the additional data, do you still feel that's the appropriate dose?

DR. SABLE: The information that we have as far as data on a 70 milligram dose is really safety because it was based in candida.. I think that the objective was to demonstrate efficacy based on the dosing regimen we selected, and through the presentation today, I think we've shown that the 50 milligram dose in aspergillus is effective in patients with poor prognosis.

Would there be a potential benefit from a higher dose? At this point we don't have the data to show that, but that there may certainly be patients who aren't clinically responding and tolerating the drug for whom an increase in dose may be appropriate.

And, in fact, in our compassionate use

study we're starting to explore that because you're right. We think at this point we do have more information, and whether 70 may be more beneficial than 50 we don't know. We don't have clinical data. We think it would be difficult to show, specially in invasive aspergillus there's a potential benefit of efficacy, but we think that there would be minimal risk to the patient from increasing the dose.

DR. SCHAPIRO: Why would there be little benefit from increasing? I mean, the majority of patients still failed therapy, right? And they tolerated the drug well. So if we have 60 percent of the patients not responding and really very nice toxicity, which appeared also not to be dose related, in most cases that would point me to say we still have a very serious infections. Most patients are still not responding. The drug is wonderfully safe. We should be giving more.

DR. SABLE: I think the points you point out are very good ones, and all I was trying to say is at this point we don't have any data to say that 70 would be better than 50. It may be, but as Dr. Perfect even mentioned in his introductory remarks, one of the other issues with these patients, particularly in the setting of salvage, is that we may

often have a point beyond which there are certain patients who won't respond.

But you're correct, and we think that looking at higher ones is something that at this point we do need to do because of the fact that we have more tolerability data that show at a higher dose the drug continues to be well tolerated.

ACTING CHAIRMAN GULICK: Dr. Graybill.

DR. GRAYBILL: I share exactly those concerns, and Dr. Sable has responded to me before that Merck is a conservative company, which is something I both admire and am frustrated by, because you've given us lovely demonstration of a safe drug, and as you have indicated so clearly, these patients are still suffering a 50 to 60 or higher percent mortality rate.

And should this drug be licensed at this time or at any other time in the future, the data that you'll come forward on safety of your recommendations for dosing for your physicians are going to be based on MICs for aspergillus and clinical experience with candida.

This is a terrible disease. This is not candida, and I just really think you need to know what the maximum tolerated dose is because it may give you

a maximum or improved efficacy in this.

This is a disease, the necrosis lung. You've got to drive this drug into tissues, and I'm just really concerned that the dose is a suboptimal dose, which is nice in one way, that you can go further. I think whenever this drug is licensed, physicians will independently go further, and they may give you that information in a format where you like it or they may give you that information in a format where you don't like it.

And this is something that would probably best be addressed in careful controls. Thinking of Dr. Kumar's comment on brain abscesses, I can just imagine that's exactly the place where a physician is going to say, "What do you mean 50 milligrams? These patients have a 95 percent failure rate. You know, damn the torpedoes. Full speed ahead."

And I think that's going to happen.

DR. SABLE: I think, Dr. Graybill, as you point out completely correctly, the initial selection of dose was based on the data that you mentioned, which was in candida infections, plus the preclinical and clinical pharmacology data.

But we don't know whether 70 would be better or what the maximally tolerated dose is. I

think that it's important to go back to the clinical data in the caspofungin study in which we have demonstrated efficacy at that dose in patients with poor prognostic factors.

I think at this point we do have enough information to say that it is important to explore higher doses, to look at the pharmacokinetics and tolerability. I think to have a head-to-head comparison as far as efficacy may be more difficult.

Doses above 70, the things to keep in mind is that the drug does not have linear pharmacokinetics, and it would have to be done in a careful step-wise approach looking both at pharmacokinetics and safety and making assessments and going forward. It would have to be done within the context of a Phase I study and then to be evaluated clinically, and that is something that --

DR. GRAYBILL: Which is what I very much hope that Merck would very aggressively pursue.

DR. SABLE: Yes. I mean, we do agree that this is something that we do need to address.

ACTING CHAIRMAN GULICK: Dr. Hajjeh.

DR. HAJJEH: Yeah, I'd like to thank Dr. Sable for an excellent presentation, very detailed, and very clear.

I have multiple questions, but also a comment. I think trying to analyze the outcome of fungal infections, invasive fungal infections, is a tremendous challenge, and this is even made more complicated by the fact that it's a noncomparative study, and you have a historical controlled group from different sites and from different management, et cetera.

But I was wondering whether you would be able to break down the number of responses among the patients who responded at least in the initial 19 and in compassionate use by the ones who at entry in the study were considered refractory because they had continued to progress versus the ones who had actually failed to do that, I mean, or were called stable disease.

And also, this breakdown was not provided for the historical controls. They were just lumped into refractory, and I was wondering if you could also break it down by among your historical patients, also how many of those had progression of disease versus stable disease and also, you know, whether this would be accounted for in the final analyses.

The other thing, you know, I also thought it would be -- again, the numbers are very small, and

also looking at the response as assessed by the expert panel among the ones with definite diagnosis versus the one with a probable diagnosis.

Also, would you like to answer each one separately? Okay.

DR. SABLE: I think that may actually be best.

ACTING CHAIRMAN GULICK: Yes, let's do that.

DR. SABLE: To go back to the first question regarding the definition of refractory in both Protocol 19 and Protocol 28, and the specific patients of whether they had progression of disease or failure to respond, I'd like to actually respond to the question about historical control first for a simple reason.

As you recall, although the patients in the caspofungin study were truly refractory or intolerant to initial therapy, the patients in the historical control study were really receiving primary therapy.

So the definitions that we used for refractory or intolerant were very conservative ones in which we say patients had no improvement after week one.

So may not have even been considered in most cases refractory in most cases by the physicians who were caring for them. So as a result of that, and the fact that of the 206 patients, almost 190 fit into the refractory category, again, remembering primary therapy, we did not go further and break down specifically patients who had not improved or who had progressed because we really felt we were comparing the overall population to those who were truly refractory in the caspofungin study.

We have looked at within the caspofungin study patients who were progressing and patients who had failed to respond at the point at which they enrolled into the study. As you would expect, the response rate is higher in patients who had failed to respond, but the response rate in patients who had progressive disease was between 25 and 30 percent, depending on whether you're looking at the original 54 or the subsequent 63, and I can show you those exact numbers if you'd like to see those.

Would you like to see?

DR. HAJJEH: Well, you know, I think it's important because you know, some of those who failed to respond might have actually ultimately responded if you gave them enough time.

DR. SABLE: Just 19. Okay. If we look at the first two -- focusing on the first two columns on this slide in patients with progression of disease, in the original 54, 34 of the patients had progression, and there's a 27 percent response rate.

With the addition of the subsequent nine patients, the response rate is 25 percent, and the patients on the end are patients who have been enrolled subsequently, which the information has not been submitted to the agency.

So if we focus on the first two columns, you can see what the response rate is.

If you can show the slide that has for the original patients progression of disease and failure to respond.

And, again, if you look at the first two columns with the patients who were considered to be failure to improve, the number of patients, but again, looking at the bulk of the patients, 40 out of 63 actually had progression of disease.

DR. HAJJEH: Okay. The other thing, again, going along the same as breakdown, the other factors that can affect the outcome in these patients are obviously multiple, and you did show one slide where you said you tried to look or consider the other

factors that affect outcome, and this was the slide where you listed all of the immunosuppressive therapies by, you know, like receiving high dose steroids or progression of underlying disease, et cetera.

I mean, again, we're talking here 26 patients among those in the 19 study that initially reviewed one, and then the 11 later.

And I would think if you start again breaking those down by the various other immunosuppressive conditions, the numbers are going to be extremely small. I mean, you're going to have maybe a couple of patients in each one of these categories, which you know, again, I mean, it's a consideration, I think, when you decide to treat a patient with Cancidas for salvage therapy.

DR. SABLE: Right. You are correct that in looking at the changes in immunosuppression -- and I can actually show you the data the way we've looked at it -- it's quite detailed as you would imagine, and there are smaller numbers of patients.

Remembering though that the patients often do have multiple prognostic factors, which is very difficult to display in looking at individual characteristics, there were favorable responses in

each of those risk groups, including patients who had high dose steroids continued, patients who received chemotherapy, had progression of their disease with either progression of their leukemias, development of graft versus host disease.

And I would be very happy to go through those and share those with you if you would like to see them.

DR. HAJJEH: You know, I think at some point I would be interested, especially you only had about 20 percent or so of your patients with neutropenia, but I was wondering among the patients who ended up responding how many of those actually had concomitant resolution of their neutropenia, or the ones who were not neutropenic had other changes in the management of their immunosuppressive condition that might also have affected their response to Cancidas.

DR. SABLE: You certainly point out some of the major challenges of dealing with these types of patients, and one of the reasons that we rely very heavily on our independent expert review, because it does in many cases come down to looking at individual patients.

If we could have the slide that looks at changes in immunosuppression, first looking at

patients who were neutropenic at baseline, defined as a neutrophil count of less than 500.

The patients who responded did have recovery of their neutrophil count before the end of therapy, but there was evidence of response prior to that recovery.

The persistently neutropenic patients, there were no favorable responses. I don't think this is completely unexpected. It's not completely inconsistent with what you would expect.

And, in fact, if you look at the patients in the historical control study, 36 individuals who had persistent neutropenia, none of those patients had a favorable response.

But it's also important to point out that in the initial 54, there was a patient who became neutropenic on therapy who had a favorable response. There are also two additional patients in the 11 supplemental patients who also became neutropenic and had a favorable response.

If we look at corticosteroids, again, looking at the patients who were -- most of the patients had those doses of corticosteroids or higher continued throughout therapy, and 25 percent of those patients responded.

If we could have the next slide, please.

Again, there were also a small number of patients who had corticosteroids started, meeting our definition of greater than or equal to 20 milligram prednisolone equivalents per day. The distribution of patients who were receiving tacrolimus, mycophenolate, other immunosuppressants, and four or five patients who received chemotherapy.

You're correct. The numbers in the cells are small, but across the different types of immunosuppression, there still were favorable responses seen.

DR. HAJJEH: Were those also available for the historical group as far as their resolution of neutropenia and other factors?

DR. SABLE: Yes, we do have that information.

Can we see the comparison slide, please?

The column on the left is as we had looked at just in the last two slides for the caspofungin study, and the slide on the right displays the information from the patients in the historical control study.

You can see, again, looking at neutropenia overall a smaller number of patients with a favorable

response, with none of the patients with persistent neutropenia responding.

In addition, there were eight patients who became neutropenic through the course of therapy, and none of those patients responded.

If we could go to the next slide, please.

We look at this similar thing across the patients who had had either continued steroids, continued immunosuppression, or changes, and you can see that across the different groups there's still a benefit with caspofungin having a higher response rate than standard therapy in patients who had continued immunosuppression.

So in the caspofungin study it's not being simply driven by the decrease in underlying immunosuppression consistent across the comparison.

DR. HAJJEH: Okay. Thank you.

Now, going back actually to the historical control group, it brings another point about neutropenia or various other immunosuppressive conditions, that it's not really just, you know, the presence of neutropenia, and I'm not sure if this is what you meant when you mentioned the different factors you controlled for in your logistic regression model.

You said neutropenia, and did you mean duration of neutropenia after they started therapy or just the presence at start?

DR. SABLE: It was actually the presence at start. All of the characteristics that were looked at were at baseline.

DR. HAJJEH: Okay, and, you know, that's another factor, I think, that we need to take into account in this analysis, is like the duration of neutropenia after either the caspofungin was started or for the historical controls, you know, the end of the evaluation.

But just a couple of final comments on the historical controls. I was wondering, you know, because everything was done in such a standardized fashion. The one difference is the outcome of patients in the historical control group was left to be assessed by the individual physicians, and it was done by the expert panel for 19.

And again, for consistency purposes, I think, you know, we should either let all of the outcomes also being assessed by an expert panel or at least a representative sample of these patients.

DR. SABLE: At the time of the submission of the application, the data that were submitted on

the historical control study were as I had presented them, which is based on investigator assessments. There has been subsequently an individual expert review of all of the cases in the historical control study.

That information has been submitted to the agency, but they have not had a chance to fully review it. There are some minor differences in how patients are classified either by diagnosis, status at week one, or outcome, but the overall conclusions of the study remain the same, and in the experts' assessments of the cases, the overall outcome, favorable response, was 16.4 percent instead of 17 percent, and his population included 214 instead of 206 patients.

I would be happy to go through the individual cases with you.

DR. HAJJEH: Oh, no.

DR. SABLE: But it's really minor differences.

DR. HAJJEH: That's okay. Just another one last kind of an epidemiologic or statistical comment.

When you showed the results of the logistic regression model with the adjusted, you know, the unadjusted first and then the adjusted analyses,

you know, to me the fact that they were so close suggests that these things that you adjusted for were not really very important modifiers of the outcome because otherwise you would have expected to see a difference in your odds ratio.

And I was wondering whether there are other factors that are actually more important as, in fact, modifiers or, you know, confounders, which we call in our typical analysis, that need to be taken care of in the analysis.

DR. SABLE: Certainly in a historical control in this type of study, there can be a number of factors which may influence outcome. The way, in fact, the predictors were identified was in looking at just the patients in the historical control study and looking at independent predictors of outcome.

The models were constructed by putting the variables in, getting to a point where there was no additional benefit from adding other variables, and that's how the different models were selected.

I think if we go back and remember the displays of the characteristics of the patient populations in Protocol 19 and Protocol 28, the characteristics which you can measure the things that we know to be influences with outcome were actually

well balanced in the two studies when we look at the baseline characteristics.

So we were actually not surprised that although the factors were driving outcome in the historical control, that because the characteristics seem well balanced that there was not a lot of movement when you were adjusting for those.

We have, in fact, also put all of the variables in the model, and you still see a similar result at the end.

DR. HAJJEH: You know, one thing we have been trying to use as a marker, and you know, as I said, these outcome analyses are very, very complicated for invasive aspergillosis, but you need some kind of measure of severity of disease at entrance into the study, and I think, you know, the one factor you included which was disseminated versus pulmonary, I think, is a decent marker, but there might be other things such as, you know -- I don't know -- it varies from disease to disease, but possibly duration of hospital stay prior to disease entry, the need for ICU admission.

I mean there are multiple other disease severity markers that could be used in such an analysis, too.

DR. SABLE: You're certainly correct in stating that there are a number of other factors, and we recognize that there are certainly limitations to historical control studies that can't be accounted for despite identifying potential sources of bias or confounding in attempting to address those. It's not the same as a prospective trial.

You certainly mentioned some of those that would be important things, very difficult in some cases to attain.

ACTING CHAIRMAN GULICK: We have time for just a couple more questions at this point.

Dr. Kumar and then Dr. Stevens.

DR. KUMAR: I'd like to ask you to clarify your response in patients with stem cell transplant. The way I've looked at your data is you had 19 patients whose underlying risk factor was ten percent transplant.

But when I looked at the outcome data, I couldn't find any data on those 19 patients, and I'd like to preface my statement that along with profound neutropenia, graft versus host disease, and management of graft versus host disease are the poor prognostic practice of patients with aspergillus.

Keeping that in mind, would you tell us

out of these 19 patients what the response was?

DR. SABLE: Yes, I can, but actually if you look in the presentation, if you pull up the slide that has outcome by underlying disease, when we were looking at baseline characteristics, all of the patients in the caspofungin study who had allogeneic bone marrow peripheral stem cell transplants also had hematologic malignancies, and if you look at the distribution, we separated those out. So hematologic malignancies without transplants and then patients who had undergone allogeneic transplants.

Within the 19 patients who had -- you're correct. It's not there. I apologize for that -- of the 19 patients, the response rate was lower than in the patients with hematologic malignancies who had not had transplants.

We can get the exact number for you. I think it was approximately 20 percent of those patients.

DR. KUMAR: Twenty percent. Did any of them have graft versus host disease?

DR. SABLE: Yes, they did. Now, many of the patients had chronic graft versus host. It was not all acute graft versus host disease.

DR. KUMAR: What was the response rate in

patients with allogeneic transplant that had graft versus host disease?

DR. SABLE: I don't have that information off the top of my head. We can get that for you, and perhaps this afternoon I can provide that to you.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Stevens.

DR. STEVENS: I just was trying to get out of the database what the overall response rate was in the historical control group, and I guess you have only analyzed refractory. Maybe you can come back to that point.

In other words, what was the response rate?

DR. SABLE: The response rate that we looked at in the historical control study was in the 206 patients who were the refractory intolerant, indeterminants excluded. That's 206 of the 229 patients.

And we went through the logic for why we selected those patients. If you look at the outcome in the 229 patients as a whole, which included, if you recall, the 13 patients who were improving and did not have elevated creatinines at week one; so patients who would not have been eligible for entry. The response

rate in the entire 229 cohort is 21 percent.

DR. STEVENS: I just wondered if John had any thoughts or you had any thought, Carole, about the 40 percent rule and that particular historical group which may have done more poorly than other groups have. Do you have any -- is that correct?

DR. SABLE: If we look at the historical control study and remember that the criteria that we used in the historical control study were designed to mirror the criteria in the caspofungin study so we required patients to have definite extrapulmonary disease and definite or probable pulmonary disease requiring culture confirmation or in our site in Europe repeatedly positive ELISAs, and that the favorable response also required radiographic improvement; I think if you look at that study the way we've defined it, it's actually similar to studies which have used similar criteria and outcomes.

If I could have the slide that compares to the study of Mary White.

Mary White did a similar study, as I'm sure you're aware, that used some of the same sites in the first half of the 1990s, which they used similar definitions for disease and outcome in a similar patient population.

The response rate on the left is the 229, as we were just discussing, and the response rate in her study was 23.4 percent. So it really does depend, I think, in part, on diagnoses as well as the types of patients that are included in the study.

In addition, if we look at the types of patients that are enrolled, that it's similar to what's been reported in the literature so that in comparison to the data overall where people have often used different definitions or different criteria for response, I think that where we can find parallels, that they're actually quite similar.

I don't know, Dr. Perfect, if you had any additional comment.

ACTING CHAIRMAN GULICK: Actually, let's -- a quick follow-up? Okay. Dr. Wong.

DR. WONG: I guess one difference is that the 40 percent refers to survival, and I didn't see survival data for your data set.

DR. SABLE: We actually used in our study as our primary endpoint favorable response.

DR. WONG: I understand. How many survived?

DR. SABLE: We do have information on survival in both the caspofungin study and in the

salvage study.

If I could have the slides on mortality, please, I want to just first point out to you what we looked at as far as looking at this during treatment and follow-up so that we can have a little bit of context for this.

Can I have the slide before that? The slide before that.

Okay. What we look for as far as deaths in the study, in the caspofungin study we followed patients, have deaths during therapy and four-week follow-up.

In addition, because of safety, deaths that were reported to us post study are also included. So the deaths that we report are all of the data that we have available in caspofungin.

In the historical control study, we have information during therapy. We also collected follow-up information at approximately 28 days. Because this was a retrospective chart review, information was available between 14 and 42 days, and there were some patients for whom follow-up information is not available.

If we can go to the next slide, and we look at mortality in the study. The mortality in the

caspofungin study was 54 percent and in the historical control study was 79 percent.

ACTING CHAIRMAN GULICK: Okay. Let me reassure people we will have more opportunities to ask questions, but why don't we take a break at this point for 15 minutes?

So we'll reconvene about 25 of 12 for the FDA presentation.

(Whereupon, the foregoing matter went off the record at 11:24 a.m. and went back on the record at 11:41 a.m.)

ACTING CHAIRMAN GULICK: Welcome back. Let's get started.

Next we're going to hear the FDA presentation by Dr. Eileen Navarro.

DR. NAVARRO: Good morning, Dr. Gulick, members of the Advisory Committee, representatives from industry, and colleagues.

Can you hear me? Can you hear me now?

My task has been made easier today by the excellent presentation by Dr. Sable and Dr. Perfect, and I'd like to thank them for having gone before me.

(Laughter.)

DR. NAVARRO: I'd like to welcome you again and hope that you enjoy the next hour.

I'd like the next slide, please.

I had also been warned by my team leader that any statement I can make from a clinical context may have significant regulatory impact. So for today's presentation, I will stick to my slides here.

Before we begin, I would like to refer you to an errata sheet that's actually in your blue folder that updates the information that we have in our background package.

Next slide, please.

I would like to start, too, by acknowledging the individual contributions of our review team, as well as colleagues in the Office of Post Marketing Drug Risk Assessment for the hard work they have put together in the last six months.

Next slide, please.

The FDA analysis I will present to day is the team's composite review of the clinical data supporting the claim for safety and efficacy of this new drug application, NDA 21-227, caspofungin acetate for intravenous injection.

This slide outlines today's presentation. The proposed label for caspofungin, highlighting the dose proposed by this indication, is presented first. Microbiology and pharmacokinetic issues relevant to

the clinical use of the drug will then be presented, followed by a discussion on the efficacy of caspofungin against invasive aspergillosis in patients with limited therapeutic options.

In the course of this presentation, I will also highlight issues in the trial design of historical controls to facilitate our understanding of the comparative efficacy of this drug, as well as to highlight issues relevant to design for other antifungals.

I will conclude the presentation with a discussion of the safety of this drug in healthy individuals, as well as in patients with fungal infections.

Next slide, please.

The application is limited to one indication, that for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies. The proposed regimen quoted in this slide consists of a single 70 milligram dose administered on day one, following by daily 50 milligram maintenance doses for the duration of therapy to be determined by the treating physician.

Next slide, please.

In patients without evidence of a clinical

response, an increased maintenance dose of 70 milligrams daily is suggested based on available safety data.

Efficacy data for this proposed higher dose has not been submitted in the new drug application.

In patients with moderate hepatic insufficiency, following the initial 70 milligram load, a reduced maintenance dose of 30 milligrams per day is recommended. No dosage adjustment is necessary for patients with renal insufficiency.

Next slide, please.

Caspofungin modulates the gene that inhibits the cell membrane enzyme glucan synthase. This ultimately results in reduced cell wall glucan composition and desmotic (phonetic) fragility of the fungal cell wall.

Time kinetic studies show the rate of healing to be slower with caspofungin compared to amphotericin B, consistent with its mechanism of action. For example, against Candida albicans where traditional broth dilution testing is relatively more standardized, caspofungin healing occurs at seven hours compared to one hour with amphotericin B.

For aspergilla species, which is the

indication we are considering today, caspofungin targets the actively growing hyphae, and the drugs, therefore, are considered fungicidal for the entire mycelium.

There is limited information on the in vitro activity of caspofungin against other fungal pathogens, such as fusarium, pseudo listeria, and new core species which can cause infections that mimic invasive aspergillosis.

Next slide, please.

As Mark has pointed out, in granular cytopenic murine models of invasive aspergillosis, caspofungin prolongs survival and reduces mycologic burden in murine kidneys.

I'd like to thank Merck first and then Dr. Walsh secondly for allowing us to present this preliminary data to you today.

Similar prolongations of survival were demonstrated in preliminary studies comparing the efficacy of caspofungin and amphotericin B in a clinically analogous model developed in Dr. Walsh's laboratory at the NCI of granular cytopenic rabbits with invasive pulmonary aspergillosis.

The mean duration of survival in this model was 6.9 days for untreated controls compared to

10.4 days and 8.8 days for caspofungin and amphotericin B at equivalent daily doses of one milligram per kilogram.

This increased survival paralleled an improvement in pulmonary infarct scores measured as the number of infarcted lobes per lung, as well as improved lung rates, as did amphotericin B compared to controls.

Paradoxically, the improvement in survival and in pulmonary measures of disease did not translate into a reduction in the lung burden of aspergillosis. Rather, an increase in colony counts to 1.9 CFU per gram of lung was seen in the caspofungin treated rabbits compared to controls.

This contrasted with the predictable reduction in colony counts seems with amphotericin B in this model. This mycologic clearing during to amphotericin did not necessarily provide a survival advantage over caspofungin, and the influenza drug toxicity and survival needs to be taken into consideration.

Caspofungin lung levels above the one microgram target were achieved with this one milligram per kilogram dose. However, an increase in caspofungin to six milligrams per kilogram in the same

model did not result in greater mycologic clearance.

Next slide, please.

Compared to healthy subjects, plasma concentrations are more highly variable for patients with fungal infections. In these patients trough levels greater than the one microgram per mL target are immediately achieved with the addition of a 70 milligram load.

CNS distribution of the drug is low in rodents and is unknown in humans.

Next slide, please.

No adjustment is needed for the concomitant use of itraconazole, amphotericin B, and mycophenolate mofetil. Tacrolimus levels are reduced in patients receiving concurrent caspofungin, and this interaction is particularly important since invasive aspergillosis can develop well beyond the initial post transplantation period when tacrolimus levels are not measured as frequently.

Because cyclosporin increases caspofungin AUCs by 35 percent, the concomitant use is currently not recommended. Nevertheless, pharmacokinetic studies indicate that cyclosporin levels are not influenced by co-administration with caspofungin.

Dr. Sable has already mentioned that

caspofungin is neither an inhibitor of nor a substrate of the cytochrome P-450 isoenzymes at clinically achievable drug levels. Nevertheless, initial population pharmacokinetic studies in patients that concomitantly receive nelfinavir, as well as a broad range of either cytochrome 3A4 inducers, indicated enhanced clearing of caspofungin ostensibly independent of the P-450 interaction.

And studies are currently underway to better understand the magnitude and the mechanism of these initial observations.

Next slide, please.

The efficacy of caspofungin in patients with invasive aspergillosis will now be presented.

Next slide, please.

As has already been stated, the clinical studies supporting the efficacy of caspofungin for this indication consist of one open label study that involved six to nine patients. The additional three patients who had been enrolled into the compassionate use programs will not be included in our presentation.

The clinical efficacy in the single pivotal trial was compared to a retrospectively reviewed historical cohort, Study 028, also known as 029 in the non-U.S. investigator sites. This study

will be referred to as the historical control throughout our presentation.

As I described the clinical studies that support the efficacy of caspofungin for this indication, I would like to point out that Study 019 was not a randomized trial and will, therefore, take the time to highlight the differences between Study 019 and the historical control.

Next slide, please.

For mucosal candidiasis, three comparative and one non-comparative study were submitted to support the evidence that caspofungin has antifungal activity. The major utility of this study for today's deliberations is in considering drug safety, and I will, therefore, discuss them in that context.

Next slide, please.

The protocol summary highlights for Study 019 and the historical control study will be presented in tandem, covering study procedures, including exclusion criteria, disease definition, response to prior therapy, timing of assessments outcome definitions and study design and analysis.

Next slide, please.

Prospective time to valuation so the patient's clinical, laboratory, microbiologic, and

radiographic status were employed for Study 019. For the historical control, conventions of clinical care dictated the timing of these procedures, and the quality of information relied on the adequacy of documentation of such procedures.

In addition, historical control design precluded the safety comparison against the drugs that are currently approved for patients refractory to or intolerant of amphotericin B.

Next slide, please.

As has also been stated so ably by Dr. Sable, the historical control employed the same strict case and outcome definitions as Study 019. However, case finding was by necessity different. Cases were identified by a review of hospital discharge registries, as well as listings in the pathology, microbiology, and subspecialty consultation departments in the ten investigator sites.

The majority of patients in both Study 019 and the historical control were identified in the four site that were common to both studies. Trained abstracters reviewed records and outcome assessments based on the abstracted data that was made by the site investigator.

Next slide, please.

I know this is a busy slide. It is intended, however, to highlight the fact that exclusionary criteria employed for Study 019 significantly differed from the historical control study.

Some of these exclusionary criteria were not present in the historical control because of practical considerations and have actually been eliminated from this list.

However, note that the more important issues that are highlighted here and are actually readable in the next slide, please -- please come to the next slide -- are not necessarily insurmountable even for a historical control design.

Study 019 excluded patients who would not have been excluded from the historical control study on the basis of baseline abnormal laboratory values, possibly indicating severe underlying disease. These included such laboratory parameters, such as hemaglobins and hematocrits, platelet counts, and INRs, bilirubin or liver function test abnormalities.

These baseline characteristics are often employed to exclude patients from prospective randomized studies, and consideration should be made for possible relaxation of exclusionary criteria to

facilitate enrollment into prospective randomized trials since these criteria are generally difficult to account for in historical control studies anyway, as has been illustrated here.

Another important consideration is the fact that patients not expected to survive at least five days were excluded from Study 019, whereas in the historical control, it could be argued that the chances of inclusion into the study were actually higher if the patient died.

Next slide, please.

Disease definitions of invasive aspergillosis modeled after the recognized Mycosis Study Group criteria were employed in both Study 019 and the historical control. Definite pulmonary and extrapulmonary infections require histopathologic evidence of tissue invasion or tissue cultures obtained through invasive procedures.

Next slide, please.

Because certain radiologic features of invasive aspergillosis are known to be predictive of true disease, for pulmonary aspergillosis these criteria together with other less invasive cultures or newer diagnostic tests were employed in the category of probable pulmonary disease.

Chest radiographs showing cavitating nodules and two sputum or one BAL in cytology examination fulfill the criteria for probable infection, whereas in expressions of more distinctive halo, crescent sign, or pleural based wedge shape infiltrates, a positive direct exam or a single respiratory culture from either sputum or BAL, or two consecutive galactomannan assays or PCRs fulfilled this criteria.

This criteria varied slightly for the historical control for only one sputum culture was required, and in one site in historical control excluded 228 patients on the basis of the single culture because of the application of the strict criteria for that site.

Next slide, please.

The same strict definition of a refractory response to prior therapy was also employed in both Studies 019 and the historical control. It bears pointing out, however, that in Study 019 the agents to which patients were considered refractory to included those currently approved for this indication, as well as other investigational azoles.

The current label of the lipid formulations of amphotericin B and itraconazole

indicate their use for patients refractory to or intolerant of deoxycholate formulation of amphotericin B.

The definition of intolerance differed between the two studies with patients in 019 identified as intolerant based on renal, as well as other infusional toxicities.

Additionally, for Study 019, a doubling of baseline creatinine or any level greater than 2.5 milligrams per deciliter on treatment or at baseline identified renal toxic patients.

In the historical controlled study, the single criteria defining intolerance was a creatinine value greater than or equal to 2.5. Intolerant patients in the historical control, therefore, may have had more significant reductions in renal function based on the single difference in criteria.

It was not possible to determine from the submitted information whether any of these patients eventually did require hemodialysis.

Next slide, please.

The timing of assessments of response to prior therapy was similar for both 019 and the historical control. A refractory response to prior therapy was assessed in both studies after at least

seven days of initial treatment, whereas intolerance could occur at any point in time, including at baseline.

Patients with baseline renal insufficiency could, therefore, theoretically receive caspofungin as initial therapy following a diagnosis of invasive aspergillosis.

Outcome assessment for caspofungin therapy was at end of therapy, whereas relapses were evaluated four weeks after end of therapy. The evaluation of relapses was not possible for historical controls.

Next slide, please.

Strict definitions of outcome were applied to both Study 019 and the historical control based on clinical, radiographic and bronchoscopic findings when they were present. Favorable outcomes include both complete and partial responses for a stable disease and clinical progression were considered unfavorable.

Next slide, please.

This slide depicts the difference in expert assessment between Study 019 and the historical control. Study 019 was reviewed by an expert panel consisting of three members who were not investigators for the invasive aspergillosis indication.

For the historical control, one of the

investigators reviewed the cases blinded as to site. Neither the expert panel nor the individual expert were blinded as to study treatment.

Next slide, please.

The mechanics of the expert panel assessment have already been discussed, and I would just like to briefly go over what they did. They actually reviewed chest radiographs, case summaries, and pathology reports, and the discrepancy in analyses were resolved at face-to-face meetings.

The majority decision then served as a final assessment.

The expert reviewer for historical control reviewed 20 data tables per patient, integrated and analyzed tabular displays while blinded to site. Any discrepancy between the site investigator and the expert reviewer was noted on a separate form.

This review has been submitted to the agency, but we have not truly had the time to actively review it because of the time of submission.

The applicant noted that the overall conclusions approximate the site investigator's assessment.

The degree of concordance for outcome assessment between the expert panel and the site

investigators were 78.3 percent for Study 019 compared to 93.5 percent between the expert and the rest of his colleagues in the historical control.

Next slide, please.

Study 019 was an estimation study, assuming an efficacy rate of at least 30 percent for caspofungin treated patients. The primary analytic population stated in the protocol was the MITT, which consisted of all patients who received one dose of caspofungin.

The expert panel population superseded the MITT as requested by the agency.

In estimating safety, a sample size of 50 patients has a 95 percent probability of detecting at least one drug related adverse event if the incidence in the entire population is greater than or equal to 5.8 percent.

Next slide, please.

In comparing the efficacy of caspofungin in Study 019 to historical controls, the applicant's primarily analysis was the proportion of success at the end of treatment. This analysis was also performed by the agency.

The applicant further performed a secondary analysis using a logistic regression model

adjusting for baseline risk variables. The agency did not perform a similar analysis.

Next slide, please.

Sixty-nine patients were enrolled in Study 019 between the period May 1998 to April of 2000. The expert panel excluded six patients, one for having received prophylactic treatment; two because they were inevaluable at the end of therapy, and three because of pathogen other than aspergillus was subsequently identified.

All further discussions regarding efficacy will be based on the 63 evaluable patients.

Next slide, please.

This diagram is borrowed from the Merck NDA and illustrates patient disposition in the historical cohort. Of the 229 patients who initially fulfilled diagnostic criteria, 206 were identified as refractory or intolerant and were evaluable at the end of therapy. I will refer to this category of patients in the rest of the subsequent efficacy comparisons as the historical control.

An additional partitioning of this category was performed by the applicant who identified five patients as intolerant only, 13 as indeterminate at week one, and 1088 as refractory.

Next slide, please.

The mean age and gender distribution of patients were generally similar between study 019 and the historical controls. There was a difference in the distribution of patients enrolled by geographic region.

There was a larger percentage of U.S. patients enrolled in the historical control study, 89 percent versus four to six percent in study 019.

This table shows the proportions of definite pulmonary and disseminated infections in Study 019 in the historical controls. A definite diagnosis was established in similar numbers between the two studies.

While the diagnosis of aspergillosis was established at autopsy in only 17 cases of the historical control, autopsy cultures also confirmed a definite diagnosis in over half of the pulmonary and extrapulmonary cases.

Next slide, please.

The proportion of patients with various underlying diseases was generally similar between study 019 and the historical control, except for a slightly higher proportion of bone marrow transplant recipients in the historical control study. The

proportion who were neutropenic or were on immunocompromising levels of corticosteroids at baseline were also similar.

Next slide, please.

This slide depicts the proportion of patients in Study 019 and the historical controls who were refractory to or intolerant of previous antifungal therapy.

As pointed out by Merck, a majority of patients in both studies consisted of patients in the refractory category with 57 percent being refractory only in Study 019 and another 27 percent being both refractory and intolerant.

There is no analogous population to this category in the historical control. Nevertheless, a review of the baseline creatinine identified 42 patients of the original 206 who were intolerant based on the historical control criteria. These patients represented about 20 percent of the patients in the historical control compared to 16 percent in Study 019.

Since only five patients were intolerant in the historical controls, the remaining 37 percent of these patients must also have been refractory and accounted for 19.7 percent of the category of

refractory only.

Next slide, please.

The proportion of patients who receive any of the available antifungal agents as prior therapy for any duration or in any combination in both Study 019 and the historical controls is presented in this slide. Over half of the patients in both studies receive the deoxycholate formulation of amphotericin B.

Itraconazole and AmBisome were more often employed in Study 019, whereas more patients in the historical control received other drugs, such as ABLC, perhaps reflecting the timing of their market availability.

Next slide, please.

This slide illustrates the proportion of patients in either study -- I'm sorry -- and the duration of therapy received depicted here in the horizontal axis. The distribution of duration of the prior therapy for Study 019 represented as the orange bars, and the total standard therapy for the historical study represented here in green bars is shown in this graph.

The shapes of the distributions appear to be initially from similar. However you will note that

there were far more patients in the historical control in the first category of zero to 25 days, whereas the proportion of patients who received caspofungin were more than the historical control in the later time points.

This resulted in the fact that patients in Study 019 were under prior therapy longer than the historical controls were under total therapy, as illustrated by the difference in mean durations of 49.8 prior therapy days' frequency versus 29.2 days standard total therapy for historical controls.

Next slide, please.

The data in this graph is presented in the same manner as the previous slide with the duration of therapy on the horizontal bar and the proportion of patients in the vertical axis.

The total duration of therapy, which includes the prior therapy and caspofungin therapy for Study 019 and the standard therapy for the historical control is show in this graph.

The mean duration of total treatment for the caspofungin treated patients was 86.1 days compared to 29.2 days for the historical controls. the largest difference was accounted for, again, in the first three weeks of total therapy.

It is known that patients who receive short courses of treatment are less likely to respond. On the other hand, we cannot discount the possibility that less aggressive therapy may have been pursued for severely ill patients or that patients may have died early for the historical controls.

This also brings into question whether the date of test of cure used in 019 is comparable to the test of cure date used in the historical controls.

Next slide, please.

The clinical success rate at the end of IV therapy was 41 percent for Study 019 compared to 17 percent in the historical control. This difference is also seen in the population of patients who are refractory to prior therapy; whereas, the intolerant patients did well overall in either study, they also represented the minority of patients in both studies.

Similarly successful outcomes in patients with pulmonary infection in Study 019 were greater than those in the historical control.

The agency agreed with the outcomes in this analysis. Additional analysis by the agency in all patients, as well as in patients that received seven days of treatment likewise confirmed the overall efficacy of caspofungin in Study 019.

However, efficacy rates were slightly lower in all patients who received the drug when patients who clinically fulfilled the strict diagnosis at baseline were proven to have infections with other pathogens and were retained in the analytic population.

Next slide, please.

This slide depicts the complete response rate for Study 019 and the historical control in relation to the overall success rates. While the successful outcome was numerically higher for Study 019, a greater proportion of the successes in the historical control were complete responses, accounting for 40 percent of successful outcomes in the historical control compared to 15 percent in Study 019, respectively.

Of the 26 patients with the successful outcome, 20 were evaluable at the four-week follow-up time point, and one of these patients had a documented relapse, whereas another patient was considered by the investigator to possibly be having a relapse.

Comparative information and relapses is limited by the fact that follow-up information was available only for a minimal number of patients in the historical control.

Three patients in the original 58 cases and one additional patient in the 11 subsequent patients had complete responses to caspofungin. The completely successful outcomes were in patients with pulmonary aspergillosis, and in one patients with a skull infection.

Next slide, please.

With possible CNS extension.

Adjunctive therapies in this complete successes include lobectomy in one patient, and concomitant itraconazole for a brief period of time in another.

One patient successfully underwent reinduction therapy and subsequent neutropenia, and three of these patients did not relapse at four weeks post end of treatment, whereas one patient died under eight days, after eight days of caspofungin therapy due to his underlying disease.

Next slide, please.

As Mark has presented, compared to historical controls, caspofungin was efficacious in patients with traditionally poor outcomes from invasive aspergillosis, such as acute leukemia, bone marrow transplantation, baseline neutropenia, and corticosteroid use.

The logistic regression analysis presented confirms the odds of a successful outcome when these predictive factors were adjusted in both studies.

Next slide, please.

This slide shows the difference in success rates of the U.S. and European patients between the two studies. The European patients appeared to have had a higher success rate than the U.S. patients in Study 019, whereas this was not evident in the historical control where a majority of the patients were obtained from U.S. sites.

This raises the question as to whether factors such as differences in the practice of patient care, different treatment regimens or different methods of asserting diagnosis or outcome may influence the results of the study.

Next slide, please.

This slide depicts the successful outcome in Study 019 and the historical control by the duration of treatment received. Merck has shown that the mean successes in the overall population appears to be higher for the caspofungin treated patients.

Among patients who receive total treatment for equivalent durations, however, the proportion of successes appear to be similar overall between the two

studies.

Next slide, please.

In Study 019, six patients were considered to have had possible CNS aspergillosis on entry into study, and two of these patients responded successfully to caspofungin. These two patients with successful outcomes at the end of treatment had received prior therapy with amphotericin B and were less significantly immunocompromised compared to the patients who failed therapy.

On the other hand, another two patients developed CNS aspergillosis while on day six and day 58 of therapy, and both patients died and were confirmed at autopsy to have CNS disease.

Next slide, please.

This slide depicts the treatment offered for 11 patients with an unfavorable response to caspofungin. Treatment was abandoned for some patients due to progression of underlying disease, whereas other patients died, and this subset of patients, therefore, represents the group for whom additional treatment was considered a viable option.

Many of these patients received the same drug that they had used as initial therapy, highlighting the limited therapeutic options for this

infection.

Three patients had adjunctive surgeries. One of these patients who discontinued caspofungin after 50 days received suppressive itraconazole and underwent the successful segmentectomy. This patient is the only successful outcome in these 11 patients.

Two other patients who underwent surgery died, one from a blast crisis following lobectomy, whereas the other patient had disseminated aspergillosis that was not clinically evident at surgery.

This experience underscores the limitations of both medical and surgical treatment in the face of well established disease.

Next slide, please.

As documented in the medical literature, the use of historical controls can lead to false conclusions of a positive treatment effect due to a number of biases making the groups noncomparable.

The next few slides discussed the sources of potential bias in historical controls as seen in this new drug application. We feel these biases can be grouped into three types: information bias, bias from secular trends in the diagnosis or treatment of invasive aspergillosis, and selection bias.

Next slide, please.

Most often information is more accurate and complete for the current treated group than for an historical control group. This better information could lead to an apparent treatment effect or the lack of a treatment effect when in actuality there is one due to a difference in the quality of information that's available.

As discussed previously, the assessment of outcome was not as rigorous in the historical control group due to a lower quality of available information. For example, the data from the historical control was obtained retrospectively. Follow-up information in the historical controlled patients is limited, and information on concomitant medications and underlying disease, both potential confounders, were not completely abstracted or available.

Furthermore, the mechanics of expert assessment also varied greatly between the two studies.

Next slide, please.

The difference in calendar time between the experience of the current treated group and that of the historical control can also make the observed difference difficult to interpret. Changes in other

factors unrelated to the treatment of interest that occur over time could produce effects that are falsely attributed to the study treatment.

The historical control group for the submission was extracted from patients diagnosed during the three years prior to and including part of the year that the Study 019 began enrollment. During this time, the historical control observed success rate increases each year from 12.1 percent in 1995 to 20.6 percent in 1998.

Market availability of certain products may explain their disproportionate use in Study 019 relative to the historical control, but the influence of this disproportionate use of this agent may also impact the observed efficacy rate.

Improvements in transplantation or oncology may not have occurred to a significant degree in the four years covered by the historical control, but the availability of new diagnostic agents, our understanding and interpretation of this new diagnostic agent, and the consequence of earlier institution of treatment afforded by the improved interpretation may have clinical significance when evaluating the impact of new treatment.

Next slide, please.

Selection bias occurs when certain types of patients are selected into the treatment group, but not into the control group or vice versa. There were far fewer European patients in the historical control group than in the caspofungin treated group, and these patients appear to have had a higher success rate than the U.S. patients.

Furthermore, differences in distribution of duration of therapy for aspergillosis was also seen. However, the success ratio stratified by total time on treatment did not differ between these studies.

The exclusion criteria for the two studies were different and more relaxed for these historical control. This may have allowed sicker patients into the control group whose outcomes could be worse. Particularly troublesome is the exclusion criteria used only in Study 019 that excluded patients who were not expected to serve at five days.

Next slide, please.

This biases could act to wide the observed effect between Study 019 and the historical control independent of treatment effect, and these differences may be responsible for some of the treatment effects seen.

While it is not clear that all of the observed treatment effect is due to caspofungin treatment, on the other hand, the degree to which these biases negate the observed effect is also difficult to quantify.

Next slide, please.

I will now shift gears and talk on the safety of caspofungin in healthy subjects and in patients with fungal infections.

Next slide, please.

Two hundred seventy-four subjects in clinical pharmacology studies and 338 patients support the safety of caspofungin. The clinical pharmacology subjects generally received one dose of the drug alone or in combination with other drugs.

In patients with fungal infections, four studies in patients with mucosal candidiasis consisting of three comparative studies and one variable dose study with 14 patients comprise the bulk of available safety information.

Safety information from the 58 patients in invasive aspergillosis represents 9.4 percent of the entire safety database.

Next slide, please.

Patient exposures based on dose and

duration of therapy is depicted in this table. Thirty-four patients received the lower dose of 35 milligrams; 233 received first dose of 50 milligrams; and 71 received the highest dose of 70 milligrams, which represented 21 percent of all exposures in patients with fungal infections.

It is important to point out that only 19 percent or 45 patients of 233 of drug exposures in the proposed dose were patients who received treatment longer than 15 days.

Next slide, please.

The overall safety of caspofungin in healthy subjects and patients with fungal infections is shown in this slide, and as expected, adverse event experiences were more common in patients with fungal infections who received multiple doses compared to healthy subjects.

Interestingly, adverse events were more often attributed to caspofungin in the patients with mucosal candidiasis over 90 percent of whom were patients with HIV infections.

Over half of the patients with invasive aspergillosis died. In the generally sicker category of patients with invasive aspergillosis, any even was more likely attributed to the underlying disease or

the accompanying therapy of underlying disease.

Only one patient in the entire safety database was considered to have had a serious drug related adverse event, and that has already been described to you by Dr. Sable.

While a greater proportion of patients in invasive aspergillosis drug discontinued drug due to an adverse event, this event was generally progression of underlying disease or aspergillosis and was not directly related to caspofungin.

Next slide, please.

The overall safety of caspofungin compared to amphotericin B and fluconazole are shown in this slide. As has also been shown by Merck, fever and infusional site toxicities, including phlebitis, were the predominant adverse events, although were less common compared to amphotericin B.

Hypersensitivity, skin reactions, as well as respiratory reactions were seen in patients with caspofungin at the much lower rate than reported for amphotericin B.

Likewise, as predictably, the renal and electrolyte abnormalities were more frequent with the standard treatment. Of note, however, when mucosal candidiasis was reported as an adverse event, this

proportion was higher for patients who received caspofungin compared to 3.4 percent and 5.4 percent for the amphotericin and fluconazole treated patients, respectively.

Next slide, please.

As mentioned by Merck, the magnitude of transaminase elevations were small, and the clinically significant elevations were even more infrequent. Four of 257 subjects in the Phase I studies had elevations greater than three times the upper limit of normal.

However, in the comparative Phase II studies, there were events where there was a more than three times elevation of upper limit of normal with a bilirubin elevation. This comprised six of 263 patients and was not significantly higher than the proportion of similar patients in those that received fluconazole.

Next slide, please.

There were rare adverse events that occurred in the clinical studies of potential significance from a safety perspective. These include the one patient who developed hypercalcemia and a raised creatinine that has also been described, as well as two other patients who developed pulmonary

infiltrates.

I would also like to state that within the comparative studies looking at the adverse event rate in patients who received caspofungin compared to amphotericin B and fluconazole, there was a higher proportion of patients who developed bronchitis-like symptoms in the patients that received caspofungin.

Histamine mediated responses were noted in the preclinical studies, and we have actually identified a case definition of possible and probable histamine mediated responses with a listing that's actually a little bit more considerable than this and includes 15 patients in one category and about six or seven patients in the other.

A recent report also documents one patient who developed shortness of breath, stridor, and rash all within ten minutes prior to infusion of caspofungin that responded to pharmacologic measures.

I would like to point out that in the safety database in both the mucosal candidiasis and invasive aspergillosis studies, most patients, at least half of patients, were in either antihistamines and corticosteroids, and the signal from a histamine mediated response may necessarily be dampened.

Next slide, please.

In summary, we have presented the proposed labeling for caspofungin and for sizing important dosing recommendations. Microbiology and pharmacokinetic issues relevant to the clinical use of the drug represented highlighting the mechanism of action and relating it to its in vitro activity and the activity in animal models.

We summarize the anticipated drug reactions and the kinetics of the drug that may impact its utility for this indication. We discuss the efficacy of caspofungin in 63 patients who were refractory to and intolerant of standard therapy, showing its overall efficacy in patients known to have generally poor outcomes.

We show the limitations of the historical control as a comparator for drug efficacy, highlighting the sources of bias that may minimize the observed difference in efficacy between the two patient groups.

We discuss the extent of drug exposures in the entire safety data base and in the patients in the invasive aspergillosis study, highlighting the limited information in the highest dose range and for the durations that are expected to be used in patients with invasive aspergillosis.

In addition to discussing overall adverse event profile of caspofungin, the comparative safety information against amphotericin B and fluconazole has also been described. The magnitude of liver function elevations, as well as other rare events have also been presented. This includes elevations of transaminases, serum, calcium or creatinine, and the development of infiltrates and possible histamine release.

We would now like to respond to any questions you may have before we break for lunch.

ACTING CHAIRMAN GULICK: Thanks, Dr. Navarro.

We have time for a few clarifying questions or points. Yes, Dr. Graybill.

DR. GRAYBILL: I would like to thank Dr. Navarro for an extremely sophisticated analysis that I think gets at some questions that Dr. Stevens and I were going back and forth. That is how is it that the control group had such a low response rate.

And a couple of things came out to me in that range that you emphasized or mentioned in your talk. This is not to say that caspofungin is not good to challenge at any rate, their response rate, but I'm still troubled by that 17 percent response.

There's a large number of patients who were treated from zero to 25 days and then much more in the control group than in the caspofungin group, and I just wondered how many of those died, had acute deaths there.

The other thing was that those who were treated in the control group with whatever were intolerant to prior antifungals, were 2.5 percent versus 15 percent of the ones that had caspofungin, and as was shown, those who really were looked at in that thing had a much higher rate of response than people who were just showing progressive deterioration.

The geographic selection is another area that's of interest, and I actually wonder if Merck could even deal with this because the European criteria are the folks that included the antigen detection and the PCRs. My suspicion is that the antigen is going to be very good. I'm a little bit more concerned about the PCR because it is so incredibly sensitive it may pick up aspergillosis in food or whatever, but these things in any case may give you an early definition of disease. Therefore, it may bias you towards having a little bit milder disease at the time a diagnosis was made and, again,

might contribute to help making the caspofungin group look a little bit better because they were caught at an earlier stage of their illness, and the historic group, of course, didn't have those kinds of things.

So I think that was a very good presentation. It does help me see some differences in this control group, and again, not at all to argue with efficacy of caspofungin, but it helps me with that 17 percent response in the control group.

Thanks a lot.

ACTING CHAIRMAN GULICK: Other clarifications? Dr. Blackwelder.

DR. BLACKWELDER: Yes. I'm trying to figure out one other potential bias that might have acted to make the historical controls, let's say, look -- it might have acted to make them different from the study 019.

The definitions of refractory you pointed out were quite different. Is it fair to think that the historical controls since they were receiving primary therapy were a different group in that in the Study 019 those were people who had already failed according to the criteria on primary therapy?

DR. NAVARRO: Would you like to respond to that, Dr. Dixon since you had looked at the actual

information and duration of therapy in both studies?

DR. BLACKWELDER: Well, I'm not referring specifically to duration of therapy, but that duration of initial therapy might be a factor, too.

DR. NAVARRO: The criteria for refractory were actually relatively standard and were used for both Study 019, as well as the historical control. Nevertheless, since a diagnosis of refractory infection requires an integration of both clinical, radiographic, and pathologic information, this was not possible in the historical control.

DR. BLACKWELDER: Right.

DR. NAVARRO: You have limited information. You're trying to analyze data from tabular displays, and that makes it difficult to actually paint a comprehensive picture of refractoriness.

This is actually acknowledged by the applicant here, and it's precisely the point in that in a historical control study, there are limitations to our interpretation of data that call into question what the observed treatment difference really is.

DR. BLACKWELDER: But let me see if I can be a little clearer. Isn't it correct -- I think it's already been pointed out -- that the investigator or

the physician treating might not have considered some of the historical controls as refractory even though they were defined that way according to the study criteria?

So they weren't actually getting what would be considered salvage therapy, whereas all of the patients in 019 were getting salvage therapy. They had already failed their primary therapy; isn't that correct?

DR. NAVARRO: Yes. In fact, I was wanting Dr. Dixon to respond to this because some of the impressions really taken from just looking at duration of therapy was that the patients in historical control are actually closest to the patients who would have been enrolled into the Study 019 by virtue of the durations of therapy that they received.

The mean duration, the mean total duration of patients in the historical control study was 29 days, and the mean duration of prior therapy before application of caspofungin therapy was very similar for Study 019, and therefore, it has been argued at least amongst ourselves that the historical control really comprised a population of patients that in their total therapy would have qualified for additional treatment with caspofungin.

DR. BLACKWELDER: Yes, but by and large, they didn't get their therapy changed; is that correct? They didn't get it changed to what would have been considered salvage therapy. They were maintained on their original therapy or some of them, I suppose, must have changed, but I didn't see that.

DR. NAVARRO: There were also modifications. In fact, there were at least three modifications, four modifications of therapy that occurred at any time point, and those 11 patients actually illustrate the number of modifications, the combinations and the durations of therapy.

We were trying to come up with a comprehensive rate to try to illustrate the actual treatments that were received and the total durations and the combinations of treatment and their modifications throughout the duration of therapy, and it was complicated.

So the presentation that we have made before you today, which in quality does not capture the differences in approaches to treatment among patients, between patients, between studies, is a simplified tabular display of the proportion of patients who received one drug versus the other. It was complicated.

ACTING CHAIRMAN GULICK: Would the sponsor like to address this issue, too, if that's okay with you, Dr. Navarro?

DR. NAVARRO: Sure.

DR. SABLE: This is Carole Sable from Merck.

And I think that as Dr. Navarro pointed out, these are some very difficult issues that we've also struggled with in both the design and analysis of the historical control study and the comparison to our caspofungin study, and there are just a few things that I would like to point out.

If you look at total duration of therapy in the two studies, it is longer in caspofungin than in the standard therapy in the historical control, but I think that there are actually several reasons for that.

If we look at prior therapy in the caspofungin study, as you recall from my presentation, in fact, 80 percent of the patients had been refractory to treatment, including a large number of patients who had had progressive disease on that therapy.

We would argue that looking at duration of treatment actually would be better to look at the

caspofungin treatment versus the standard therapy. Again, as Dr. Blackwelder pointed out, one of the other issues is salvage versus primary therapy, and we think that's one of the biases that's against caspofungin because at a one-week assessment, every time we had a decision to make, we tried to take the conservative one.

The only assessment for refractory or intolerant was at one week of therapy, and I think that most of the people in this room who have cared for these patients would actually say that you don't really expect most patients to have improved by that point.

We excluded patients who died after receiving fewer than seven days of therapy to eliminate that piece. Then if you look at duration otherwise, the durations of therapy in caspofungin and standard therapy are similar.

At some point there will be a dichotomy because the response rate in caspofungin treated patients was 41 percent versus 17 percent in the historical controls, and so both the definition of refractory that we used was conservative and, we think, a bias against caspofungin, as well as the fact that we're talking about salvage versus primary

therapy being a bias against us.

The one thing I would like to show you is a Kaplan-Meier plot of the mortality in the two studies. So we can actually look at times of death in the two studies.

This shows from Protocol 19 mortality from day one of therapy. The one thing I want to point out is, as Dr. Navarro mentioned, one of the criteria for the prospective study was that we wanted to have patients enrolled for whom there was some expectation that the patients would have a chance to respond.

However, although we had that criteria for some expected survival in the study, ten of the 30 patients who died during treatment died after receiving fewer than seven days of treatment with caspofungin.

The line in blue actually includes all of the deaths. What we've also done in this graph is the patients who were lost to follow-up, who were discharged to Hospice, are being counted as being dead even though we do not have information to that fact. We assume that they have died.

The yellow line displays the historical control study beginning at day seven, the day at which the patient's work would have been considered

potentially eligible, and what you can see is that the early part of the curve actually is parallel, and where it splits is later on.

And we would argue that that is because the patients were actually showing response to caspofungin and were surviving longer because they were having benefit from that therapy.

So we think it is a very difficult issue, but this is the way we've tried to look at the information.

DR. BLACKWELDER: Could I follow up just briefly on that?

ACTING CHAIRMAN GULICK: Yes.

DR. BLACKWELDER: What I was trying to get: is there a subset that you could identify in the historical control population that received what would have been considered salvage therapy, or is that possible to ascertain from your records?

DR. SABLE: One of the difficulties that we had in looking at a retrospective chart review is, as Dr. Navarro mentioned, the decision to call someone refractory actually requires several pieces of data which are very difficult to gain from a retrospective review.

The other point to that is that patients

often had changes in therapy that were either additions, adjustments in dose, and we were not able -- we did not go back and specifically try to identify a subset of patients.

I don't know if Dr. Navarro wants to comment on any analyses that the FDA might have done to that regard.

DR. NAVARRO: In the briefing package, we actually tried. We have summarized an analogous population of patients who we had information as to allow us to on a limited basis define the fractoriness or intolerance, and the general conclusions actually were similar. The numbers do not differ.

ACTING CHAIRMAN GULICK: Okay. This seems like a good place to stop. We will have ample opportunity to ask some more questions after lunch before we get into the specific questions posed to the committee.

So we're breaking, and we will resume at 25 of two.

(Whereupon, at 12:44 p.m., the meeting was recessed for lunch, to reconvene at 1:35 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:44 p.m.)

ACTING CHAIRMAN GULICK: Welcome back from lunch, everyone. We're going to begin.

The next part of the agenda is dedicated to the open public hearing. We actually do not know in advance of anyone that wants to make a formal presentation, but if someone would like to make a presentation, I would call on you now to stand up and come to the mic.

(No response.)

ACTING CHAIRMAN GULICK: That concludes the open public hearing portion.

(Laughter.)

ACTING CHAIRMAN GULICK: So now we'll go to Mark Goldberger for the charge to the committee.

DR. GOLDBERGER: Are we able to put the questions up on the Proxima?

Well, basically we're asking three questions of the committee. The first question is: do the data presented demonstrate that Cancidas is safe and effective for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of standard antifungal therapy?

And in the discussion, although obviously

you're free to comment on all of the issues that you deem relevant to this decision, we would like you to particularly be sure that you touch upon the following:

The amount, e.g., the doses and duration of safety data;

The restriction on the population, refractory and intolerant;

And the historical control data.

Now, as you think in terms of these issues, there's a couple of things that I'd like to bring up. One is, first of all, obviously you just want to be thinking of them in terms of the basic approval decision, i.e., whether the product is safe and effective.

If, you know, your determination is yes, but there are some concerns, highlighting those concerns can be helpful because we can often address those in the product labeling, and I think one issue, for instance, that came up this morning is the issue that there's likely to be off label use at a higher dose than what the product leveling will be, and how much a concern this is and any suggestions about potential labeling for this, for instance.

Related though to these issues also, as

I'm sure many, if not all, of you are aware, is the fact that we often work with the sponsor on developing what are called Phase IV commitments, i.e., studies that are to be done after the original approval decision since we all recognize that information on any product is incomplete at the time of the original approval, and generally the only question is how incomplete it's going to end up being.

Therefore, if you have specific recommendations with regards to any of the topics I just outlined and/or any other studies, et cetera, that you think would be helpful, you know, please include that in your discussion.

Now, if the answer to the issue of safety and efficacy is no, then we would like you to spend some time talking about what additional information would be required in order for this product to be approved.

Our second question is: the indication discussed today is for patients who are refractory to or intolerant of standard antifungal therapy. What additional information, preclinical and/or clinical, would be needed to support the indication of initial therapy/first line treatment of invasive aspergillosis.

And I think, again, this is the question that, first of all, you know, obviously can be discussed with relation to the product in question today, but it can also be discussed more broadly since, as I mentioned at the beginning of the meeting, there is a considerably amount of interest among the pharmaceutical industry in developing products for this indication.

You know, as we've talked, it is not an easy indication to study. We've also already had a fair bit or discussion about the limitations of historical controls, raising the issue of randomized controls and the difficulties in doing them. So we think that this is an important, you know, issue to be discussed.

If you wish to talk about the desirability, et cetera, of doing these types of studies for the product in question today, I think that would be entirely appropriate as well.

Our last question is really a more general one to help us with advice to the pharmaceutical industry, investigators, et cetera, and that is: what additional advice does the committee have regarding the design of future studies needed in the development of therapeutic agents for initial therapy and therapy

of patients, refractory or intolerant to other antifungal therapies, in patients with pulmonary and/or disseminated aspergillosis.

And again, you know, the advice can be on any topics that you deem to be appropriate. However, things that we felt might be of interest to include in the discussion include the role of animal models, the impact of whether the agent kills the organism, i.e., is fungicidal, or inhibits its growth, is fungistatic.

As you know, there was some discussion this morning of some of the difficulties in utilizing these terms with regards to aspergillus. So any comments you'd like to make in that regard would also be welcome.

The relative importance of microbiologic endpoints compared to clinical endpoints in evaluating the agency's efficacy in a clinical trial. Obviously this is an issue at times certainly with aspergillosis, with a difficulty sometimes in getting adequate specimens, particularly perhaps adequate specimens in follow-up.

And finally, again, the choice of the control regimen, historical versus active control, i.e., for instance, a randomized trial, recognizing not only, you know, the issues of limitations of

historical control, but it would probably be helpful to talk about any obstacles that exist in terms of doing a randomized study, and obviously there are some, and suggestions that you might have in terms of ways to minimize or overcome those obstacles.

Basically those are our questions. If you require any further clarification during the discussion, you know, we'll be happy to provide that.

And to commemorate the fact that I've just finished the first question, it is now briefly up there.

DR. MURPHY: Leave them up, leave them up.

DR. GOLDBERGER: Yeah, and you can leave it up, Karen.

DR. MURPHY: Karen, leave them up as he goes through them.

ACTING CHAIRMAN GULICK: Yes, I think it would be helpful to leave them up.

I think the way that I would like to structure this is to go back to the committee and give an opportunity for people to ask additional questions before we begin to consider the questions posed to us.

Dr. Stevens.

DR. STEVENS: Yes. I have a question that relates to the preclinical safety data and may

actually be relevant to the discussion that went on this morning about the fact that the higher doses may be used in the future in clinical trials.

Our lab reported that when another drug in this class, another echinocandin drug LY30366, is given to mice with steroids, it produces a lethal effect, and so this question is for the FDA, not for Merck.

Should it be of interest to know whether that lethality and that lethal toxicity is a property of the class?

And nothing that was presented here today addressed that issue, and I'm just wondering what the FDA thinks about that.

DR. MURPHY: I don't think we have our preclinical people here, but I can tell you that if you have this observation and this data and you think it's something that we should consider in asking for additional studies, it does not have to be in human, the additional studies that we would ask.

DR. STEVENS: Right, but there are two -- I mean, their data is published actually. I mean, it's not data that isn't available to you. It's published information. In fact, I sent it before publication to the FDA.

But that's one way to address that, would be in animal model studies of a similar design, and the other would be to go back and extract from the clinical data the toxicities that were seen in the subgroup of patients who received steroids. We didn't have that broken out this morning either.

ACTING CHAIRMAN GULICK: Dr. Sable, would you like to address this?

DR. SABLE: Yes. Thank you.

ACTING CHAIRMAN GULICK: It looks like you would.

(Laughter.)

DR. SABLE: Actually to address Dr. Stevens' point, we have actually looked at this carefully because of your article and the observations that you reported.

And just to let people know, the study to which Dr. Stevens is referring, when mice of a specific strain were pretreated with cortisone, hydrocortisone, or triamcinolone, but not dexamethasone, there was a higher incidence of mortality in those mice.

We've looked back at our preclinical studies, and in fact, there was a murine model which was conducted by Dr. Graybill in which the mice were

pretreated with hydrocortisone and given then caspofungin, and there was no effective mortality seen.

But now, of course, we do have clinical data, and of the 330 patients who have received treatment with caspofungin, 63 patients received prior treatment with corticosteroids of a varying type prior to treatment. Sixty-one received concomitant corticosteroids.

The minority of those patients, in fact, fewer than ten in each group, received dexamethasone as the only corticosteroid, and we've actually done through and have looked at the safety data, have not seen any association of adverse experiences with our drugs in corticosteroids at no settings.

But we realize when Dr. Stevens published that paper that that was a concern, and we needed to address it.

DR. STEVENS: I just want to emphasize that the lethality that we saw was not in infected mice. I mean, we saw it in infected mice, too, where there was accelerated mortality, but you can demonstrate the phenomenon in uninfected mice as well, and I think it might be relevant to go back and do so more preclinical studies along those lines because of

the issue that came up that higher doses may be used in the future.

And maybe there is no problem that's been seen in your analysis of the clinical database with the doses so far, but that could change as people in the field start to use higher doses.

My take on looking at the clinical safety data is there's an awful lot of deaths in patients who are receiving the therapy for aspergillosis, and it may be 50 percent of the patients died. It may be very hard to tweak out what could be a toxicity related to a drug-drug interaction when the patients are on ten different drugs and have three underlying diseases and five reasons for dying.

So it may be very hard to tweak out that information in that subset of patients, and I think it's comforting, very comforting, the results that you showed us with respect to efficacy, particularly in the patients who were getting more than 20 milligrams of steroid. So that's very promising.

But, again, the doses that were used in mice may be much higher than what's been used in humans up until now, but may not be true of the doses that are going to be used in human coming a little bit further.

DR. SABLE: Just in one follow-up comment to Dr. Stevens, certainly in patients with invasive aspergillosis, making a determination of cause of death is complex, as you are well aware. We had patients not only in the aspergillus studies, but also in the candida studies as well, where they were much less acutely ill.

When we looked at the cases because of the numbers, it was possible for us to go through them individually, and the cases of patients who died certainly if you look, there were 50 percent mortality, not just during treatment, but treatment, four-week follow-up, even deaths reported post study.

We went through and looked at the causes of death reported by investigators, whether patients had autopsies and what information was available from those. So we were able to on an individual case basis go back and look through all of those data.

So I can't tell you a specific cause, but when we look at patients who received steroids versus those who didn't, we did not see any differences with regard to mortality.

ACTING CHAIRMAN GULICK: A follow-up, Dr. Graybill?

DR. GRAYBILL: I notice that Dr. Walsh is

here, and he's had lots of experience with animal models, including with these drugs, and I was wondering if Tom might be able to offer some insight from his own studies on this issue.

DR. WALSH: Dick and David, thank you for bringing up that question.

In both our persistently neutropenic rabbit models of invasive pulmonary aspergillosis, as well as the analog for graft versus host disease immunosuppression, methylprednisolone, cyclosporin at five milligrams per kilogram per day of methylprednisolone, we've studied each of the echinocandins that are currently in clinical trials, FK 463, VER 002 and MK 0991 or caspofungin, and we have not seen any evidence of a dose dependent toxicity.

There was a suggestion in the neutropenic model that at 20 milligrams per kilogram there was a slight increase in mortality. We notice that the lungs at that time were slightly more edematous, but beyond that, we could not identify any electrolyte abnormalities. We do full CDC and chem. panels on the animals every five days and could not discern any abnormalities.

But beyond that, we have gone up to six,

ten milligrams per kilogram on the VER 002. Certainly on the FK 463 we've gone to 20 milligrams per kilogram, did not see mortality or increased mortality there, and the same on the caspofungin.

So it's hard to discern a relationship of steroid echinocandin interaction, but it certainly doesn't exclude the possibility, but we just haven't seen a classic dose dependent toxicity using a given biochemical parameter similar to what we could see with amphotericin B and nephrotoxicity.

ACTING CHAIRMAN GULICK: Dr. Fletcher.

DR. FLETCHER: I have multiple questions. Let me start with body weight. The dose proposed is a standard dose across all body weights in adults, and in the background information provided by the sponsor, it's noted that concentrations are higher and more variable in lighter patients and subjects, but that the standard dose is still fine, and I'm not concerned about lighter patients having higher concentrations, but what about heavier patients having lower concentrations?

And I'm wondering related to that, in your analyses of the data then, for example, in the logistic regression, did you look at whether body weight, in particular, heavier patients, had any